Management of Latent Tuberculosis Infection in China: Exploring solutions suitable for high-burden countries

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Abstract

China is one of the countries under high burden of tuberculosis (TB) and latent tuberculosis infection (LTBI). It is newly estimated that China had the highest LTBI burden in the world with approximately 350 million persons living infections. Guidelines and strategies for management of LTBI suitable to China have not been systematically developed yet. The prevalence of LTBI in China was overestimated by TST as compared to IGRA. A population-based study found IGRA positivity rates ranged between 13.5% and 19.8%. The annual TB infection rate in rural population was 1.5% based on persistent positive IGRA results in converters. The development of active TB from LTBI in the general rural population was 0.87 per 100 person-years in the first 2 years among individuals who newly converted IGRA positive. TB control in students was paid more attention by the government which also improved LTBI management among students with close contact to active TB patients. A 3-month regimen with twice-weekly rifapentine plus isoniazid ($3H_2P_2$, both with a maximum dose of 600 mg) has been practiced for LTBI treatment in China for years. With respect to LTBI management in populations using immune inhibitors, an expert consensus on TB prevention and management in tumor necrosis factor antagonist application was published in 2013 in China. In order to achieve the global goals of the END TB, China needs innovative ideas and technologies to control active TB disease by management of LTBI, such as

identification of populations for testing and treatment of LTBI, selecting and developing reliable LTBI tests, exploring safe and effective preventive treatment tools, and establishing LTBI management system.

Keywords
China; latent tuberculosis infection; burden; prevalence; management

Introduction

China is one of the countries under high burden of tuberculosis (TB) and latent tuberculosis infection (LTBI). According to the *Global Tuberculosis Report 2019* published by World Health Organization (WHO) [1], TB incidence rate in China was 61/100,000 and TB incident cases of China accounted for 9% of the global total in 2018. In addition, it is newly estimated that China had the highest LTBI burden in the world with approximately 350 million living infections [2]. By now, it has been widely accepted that managing active TB and LTBI are equally important for achieving the goals of the WHO End TB Strategy [3]. In 2015, WHO released *Guidelines on the Management of Latent Tuberculosis Infection* to provide guidance for LTBI management in high-income or upper middle-income countries with an estimated TB incidence rate of less than 100 per 100,000 population, including China [4]. Since then, LTBI management has been given new historical mission, besides protecting at-risk individuals, as to decline TB incidence in community level. However, only targeting the high-risk populations recommended by WHO guidelines, such as people living with HIV and household close contacts, for LTBI management might not achieve significant decline on TB incidence in China. Take HIV infections for example, in 2018, the contribution of incident cases from people living with HIV in China was only 2%, but it was 10% in America, 12% in Europa and 25% in Africa, respectively [1]. Therefore, selecting at-risk populations for LTBI testing and treatment should be adapted to the national epidemiology of TB, the availability of health resources and other local determinants. However, such guidelines and strategies suitable to China and other high burden countries have not been systematically developed yet.

LTBI Burden in China

LTBI is a state of persistent immune response to simulation by *Mycobacterium tuberculosis* (MTB) antigens with no evidence of clinically manifest active TB. Currently, there is no gold

standard for diagnosis of LTBI. Interferon-γ release assay (IGRA) and tuberculin skin test (TST) are two available LTBI testing methods based on cellular immune responses. It was estimated that 44.5% of population were infected with MTB by TST from the forth National survey in 2000[5]. In 2013, Gao and colleagues started a population-based multicenter prospective study to assess LTBI burden in rural China. They found the prevalence of LTBI in China may be overestimated by TST as compared to IGRA. The baseline data of the study showed, between the four selected study sites, age and gender standardized TST (≥ 10mm) positivity rates ranged from 15.5% to 41.7% but IGRA positivity rates ranged between 13.5% and 19.8%[6]. It has been well known that TST overestimated LTBI numbers because its performance was significantly affected by bacillus Calmette-Guérin (BCG) vaccination and some nontuberculous mycobacteria (NTM) infection. In contrast, IGRAs are unaffected by previous BCG vaccination or exposure to most NTM because they use antigens coded by MTB complex specific regions of difference that are absent from most NTM and from all strains of BCG. Therefore, epidemiological studies addressing LTBI prevalence in the general population showed good consistency when using IGRAs [6].

With the availability of IGRAs in China, the prevalence of LTBI has been re-estimated recently in several specific populations. LTBI prevalence among household contacts was found to be relatively high (32%-48%) [7] [8]. TB infection rate in healthcare workers (HCWs) ranged from 15% to 70% with respect to the level and the location of the hospital [9] [10]. IGRA positivity was observed to be lower than 10% in schoolchildren and adolescents [11] [12]. Among people living with HIV infection, the prevalence of LTBI was found to be 9% in a population of men who have sex with men (MSM) [13]. Such a low prevalence might be at least partly explained by immunological deficiency which decreased the sensitivity of IGRA and thus increased the number of false negatives.

As in other countries, very few prospective studies have been conducted in the general population to estimate the annual risk of TB infection. In the study of Gao et al, among 12,749 eligible participants identified as IGRA negative at baseline survey, 390 (3.1%) were IGRA converters in one year. However, during the second year's follow-up, only a half of the converters were found to be consistently positive and the others got reversion. Hence, they estimated that the annual TB infection rate in rural population was 1.5% based on persistent positive IGRA results in converters [14] Age growing, male gender and close contacts with

active TB patients were found to be independent risk factors for TB infection. Thus, the elderly were suggested to be one promising target population for infection control due to their higher acquisition and persistence of infection found in this study.

The development of active TB from LTBI in the general rural population was followed by Gao and colleagues as well [15] [16]. They observed that the incidence rate of active TB was 0.87 per 100 person-years and 0.26 per 100 person-years in the first 2 years (2014-15) and in the latter 3 years (2016-18) after baseline survey (2013) among individuals who were IGRA positive, respectively. Their prospective results persistently suggested that about 30% TB incidence might attribute to a history of prior TB in rural China. Based on the findings of this prospective study, they suggested that to achieve the target of decreasing incidence at a community level in China, individuals with a history of prior TB should be considered for LTBI testing and treatment, in addition to those with likely recent infection, such as close contacts of patients with active TB.

Current situation of LTBI management in China

In China, at this stage, LTBI management is not an important part in the national TB control strategies. People living with HIV, children <5 years old with contact to a pulmonary TB patient, clinical indications such as silicosis, anti-TNF treatment, dialysis and transplantation have been recommended as target populations for LTBI treatment. However, it has not been carried out systematically due to lacking national guidelines. The population of China is huge and the size of LTBI population is astonishing even estimated by IGRAs, plus the risk of re-exposure is still high, it limited the feasibility to scale-up LTBI testing and treatment in China.

Nevertheless, in China, it was estimated that there were 13,900 children under 5 years old as household contacts of a bacteriologically confirmed pulmonary TB case but were not systematically covered by preventive treatment in 2018[1]. By December 2018, there were 1,250,000 people living with HIV in mainland China. In any case, these two populations with high likelihood to develop active TB after infection should be widely protected by LTBI treatment.

Fortunately, TB control in students was paid more attention by the government which also improved LTBI management among students with close contact to active TB patients. *Code*

of Practice for Prevention and Control of Tuberculosis in School [17] clearly requests that children in kindergarten, primary school and middle school who are 15 years younger should take TST in admission, anyone with TST strong positive (>15mm or with blister) should take chest X-ray for active TB screening. In addition, high school and college students ⩾ 15 years should take chest X-ray for active TB screening directly in admission. Annual routine examination for teachers should include TB screening as well. Once an active TB case confirmed, all the close contacts including roommates, classmates and teachers would be investigated and screened for active TB and LTBI. Individuals with TST strong positive and normal chest radiography will be recommended for preventive treatment. Although the technical pathway needs improvements, such as TST might introduce many false positives for LTBI management, this action has played important role to control TB epidemic in schools. In schools, a 3-month regimen with twice-weekly rifapentine plus isoniazid ($3H_2P_2$, both with a maximum dose of 600 mg) has been practiced for LTBI treatment in China for years. A non-RCT has been conducted for tuberculin skin test-positive college students using $3H_2P_2$ (1948 treated and 1765 untreated); the occurrence of liver dysfunction (ALT/AST higher than normal level) was reported to be 2% and the protective rate was observed to be 75% during 4 years of follow-up [18]. Compared with WHO recommended 3HP (3-month, once-weekly rifapentine plus isoniazid, both with a maximum dose of 900 mg), $3H_2P_2$ was determined mainly based on the following two points. 1) It was reported that the genetic background, such as drug-metabolising enzyme gene polymorphisms, might contribute to various risks of anti-TB drug-induced liver injury [19]. 2) Asians have been reported to carry a higher frequency of rapid acetylator genotypes of N-acetyltransferase 2 (～50%) than Caucasians (～5%). Rapid acetylators are prone to treatment failure, probably due to insufficient exposure to isoniazid [20]. Therefore, reduced single dosage and increased frequency were adopted in $3H_2P_2$.

With respect to LTBI management in populations using immune inhibitors, an expert consensus on TB prevention and management in tumor necrosis factor antagonist application was published in 2013 in China [21]. It suggested that all of the patients who prepare to take TNF antagonist should be identified for LTBI or prior TB. The screening items include detailed medical history to evaluate risks of TB, chest x-ray or Chest CT if necessary, TST and IGRA. Preventive treatment should be given to the individuals with LTBI using regimens of 6HR (6 months, once daily isoniazid with a dose of 300mg plus rifampin with a dose of

450mg) or $6H_2P_2$ (6 months, twice-weekly isoniazid plus rifapentine, both with a maximum dose of 600mg).

Developing LTBI management strategies suitable for China

Indeed, there are many challenges to effectively manage TB and LTBI in the meantime for high burden countries with limited resources. But in the absence of an effective vaccine, it is so important to start such a virtuous circle to combine prevention with treatment. It is well known that population based LTBI testing and treatment is not feasible, but for infected individuals under high risk for progression to active disease, the benefits are greater than the harm. Therefore, LTBI management should be at-risk populations centered whether in high burden countries or in low burden countries. Furthermore, treatment should be delivered effectively to guarantee that the majority of those starting a treatment regimen will complete it with no or minimal risk of adverse events. Nevertheless, the current situation is LTBI tests are imperfect, there are risks of serious side-effects for preventive chemotherapy, and the cost of management is relatively high based on currently available tools. In China, we need innovative ideas and technologies to control active TB disease by management of LTBI.

1. Identification of populations for testing and treatment of LTBI. Such populations should share a common feature that is at high risk of infection and disease development (such as close contacts of active TB patients, HIV infections, immune inhibitors users, HCWs). However, in high burden countries in order to achieve the goals of reducing incidence, such populations, at least partly, could influence TB incidence in a community level as well. Therefore, epidemiological studies are needed to identify such targets from the perspective of public health. By the way, artificial intelligence technology such as electronic chest radiograph reading system would improve the feasibility of population based screening for at-risk subgroups such as those with abnormal chest x-ray.
2. Selecting and developing reliable LTBI tests. Considering BCG vaccination has been included in the national immunisation program in China for almost 40 years, we should interpret TST results with caution especially for children and students. A two-step approach has been suggested, for regions with BCG vaccination but resource limited, to test LTBI by IGRA in TST-positive subjects. It has also been found to be suitable for using in Chinese adolescents [22]. In addition, the development of novel specific skin test based on ESAT-6 and CFP10 antigens provided more choice for LTBI testing [23].

3. Exploring safe and effective preventive treatment tools. The efficacy of currently available preventive treatment regimens ranges from 60% to 90%. However, none of the WHO recommended regimens have been evaluated in Chinese populations by randomized controlled trial (RCT). Gao et al conducted a RCT to study the performance of 3HP among individuals with LTBI (aged 50-69 years) in general population20, but due to the increasingly rapid growth and unexpected high frequency of adverse effect, the treatment was terminated early. However, a 6-week twice-weekly rifapentine plus isoniazid regimen (both with a maximum dose of 600 mg)) showed a protective efficacy > 60% in this study [24]. In addition, a 1-month regimen of rifapentine plus isoniazid was found to be noninferior to 9 months of isoniazid alone for preventing TB in HIV-infected patients [25]. Such innovative regimens with ultrashort courses and optimized use of drugs are a significant advance in vulnerable populations and in resource-limited areas. Very recently, it was reported that vaccination with M72/AS01E provided protection against disease progression from LTBI for at least 3 years [26]. The development of such novel tools will provide great support for LTBI management in high-burden countries.
4. Establishing LTBI management system. Currently, TB management system mainly includes two parts, one is the designated hospitals responding for clinical treatment of active TB and another is the centers for disease control and prevention (CDC) responding for patient management including the implementation of Directly Observed Therapy (DOT). To manage LTBI, it will also need combination of resources from hospital and CDC. Considering LTBI population size is much larger than TB patients are and then needs much more public health resource, community doctors might be main strength to implement LTBI management.

In summary, LTBI testing and treatment in individuals at-risk of developing active TB has been proved to be an effective strategy for TB control in low-burden countries. In order to achieve the global goals of the END TB, China should act on LTBI management as well to protect high risk individuals and to decline community incidence. But innovative work is needed to develop guidelines on LTBI management suitable for China under high burden for both TB and LTBI.

Conflict of interest statement

All the authors have no competing interests to declare.

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